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THE COUNCIL FOR TOBACCO RESEARCH -- U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

RECEIVED
AUG 12 1974

APPLICATION FOR RESEARCH GRANT
(Use extra pages as needed) DATE: 8/5/74

1. Principal Investigator (give title and degrees):

Walter B. Essman, M.D., Ph.D.
Professor of Psychology & Biochemistry

2. Institution & address: Queens College of the City University of N.Y. 65-30 Kissena Blvd. Flushing, New York 11367 and The Research Foundation of the City University of N.Y. 1411 Broadway New York, New York 10018

3. Department(s) where research will be done or collaboration provided:

Psychology, Biochemistry

4. Short title of study: "Studies of Nicotine Action Upon Memory Consolidation"

5. Proposed starting date: January 1, 1975

6. Estimated time to complete: 36 months (3 years)

7. Brief description of specific research aims:

The present protocol represents an extension of research investigations of regional, cellular and subcellular central nervous system sites altered by nicotine and/or its metabolites and the process of memory consolidation (i.e. neural events by which the memory trace becomes fixated and stored within the central nervous system). Specific studies will further explore the hypothesis that nicotine and several of its biologically active metabolites may serve to block the molecular effects of 5-hydroxytryptamine at selected receptor sites. The studies will further deal with mechanisms by which nicotine and its metabolites prevent 5-HT induced inhibition of protein synthesis which has been shown to serve as an amnesic event. Specifically, this hypothesis will be investigated on the basis of:

1) developmental effects of nicotine and metabolites;

2) strain differences in nicotine and metabolite effects; 1003544434

3) strain and age interactions and memory consolidation;

4) and, the inter-relationship of age and strain variables in the process of memory consolidation effects of nicotine and metabolite effects on a cellular level.

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7. continued:

Because the neuropharmacology of nicotine appears significant in that it offers import insight into basic mechanisms of memory consolidation, the present project also holds further significance in the clarification of those molecular mechanisms identified with disruption of the memory consolidation process, i.e., retrograde amnesia.

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8. Brief statement of working hypothesis:

Nicotine and several of its biologically active metabolites capable of exerting central nervous system effects are capable of interfering with receptor effects of brain 5-hydroxytryptamine which, in appropriate circumstances, inhibit synaptic protein synthesis and interfere with the memory consolidation process. Thereby, such compounds can alter the time course over which memory consolidation occurs and facilitate the process. Such facilitation of memory consolidation by nicotine and metabolites will be regulated by the age of the animal within specific strains; i.e., certain strains will be more or less susceptible to the facilitative effects of these drugs. Similarly, the interactions between nicotine and metabolites of 5-HT induced inhibition of synaptic protein synthesis will be age and strain dependent.

9. Details of experimental design and procedures (append extra pages as necessary)

Mice of all three strains to be utilized in these studies will be conditioned to establish a stable passive avoidance response conditioned in a single training trial, utilizing a method (Essman and Alpern, 1964) established as effective for this purpose. The amnesic effects of a variety of agents and/or events presented in close temporal proximity with the acquired experience in this situation results in a reduced incidence of retention measured 24 hours or more later. Amnesia in this situation is defined by inability of the animal to perform the avoidance response to which it was previously trained.

Mice will be utilized from stock either obtained commercially or specially bred in institution vivarium facilities in order to maintain persistent controls over age differences. The strains to be utilized in the present study will be CF-1S (Carworth Farms), which have been previously utilized in past studies; C57/BL6J, a mouse strain previously shown to exhibit superior conditioning ability and long term retention of conditioned behavior, in addition to showing a decreased

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susceptibility to the amnesic effects of several training treatments which usually result in a retrograde amnesia. The third strain of mouse to be utilized in the series of experiments will be DBA-2 strain, which has proven to be a poorly conditioned animal that shows a markedly increased susceptibility to the amnesic effects of several agents or events.

Animals from the designated strains will be utilized at specific ages ranging from 16 to 35 days and these will deal with (1) The effects of nicotine and active metabolites such as cotinine and 3-pyridylacetic acid upon the retrograde amnesic effects respectively induced by: (a) transcorneal ECS (see Essman, 1973, #5, Pg. 3b; (b) intrahippocampal 5-hydroxytryptamine (Essman, 1973, #9, Pg. 3b2, and (c) intraperitoneal injection of short-chain fatty acids. All three of the above treatments have been shown to exert a time dependent retrograde amnesia in CF-1S strain mice and also to elevate brain 5-hydroxytryptamine content and cause an inhibition of brain protein synthesis. Extensive publications have supported these phenomenon in the case of the first two treatments and the third treatment holds particular significance in that increased short-chain fatty acid concentration has been implicated in several clinical entities, such as Wilson's dieease, hepatic coma, hepatic cirrhosis and metabolic convulsions -- all of which involve altered sensorial and memory function. Intraperitoneal injection of 15 mg/kg of octanoic acid induces coma rapidly (70.3 ± 4.6 seconds with an average duration of 17.7 ± 3.7 minutes); such short-chain fatty acid induced comas produce a retrograde amnesia, elevation of brain 5-hydroxytryptamine and inhibition of protein synthesis which is antagonized by both nicotine as well as its major metabolite, cotinine.

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In the proposed experiments, mice from three designated strains will be treated either immediately, 60 seconds, 10 minutes, or 60 minutes following conditioning as previously described, and a temporal gradient for the retrograde

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amnesic effects of such treatments will be generated as a function of age.

Based upon such baseline data, the dosage and drug treatment interval for nicotine, cotinine, 3-pyridylacetic acid, will be assessed in experiments that will allow for (2) Specification of the temporal relationship between nicotine and/or metabolic effects upon cerebral amine metabolism and amine metabolite inhibition of protein synthesis.

Studies will specifically test the hypothesis that strain and age-dependent antagonism of retrograde amnesia by nicotine and several of its active metabolites depends upon the ability of this drug to block metabolic events associated with the amnesic stimulus. Such events specifically included the relevence and increased site accumulation of 5-HT at the presynaptic nerve ending and mediation, thereby of unhibition of protein synthesis in these regions. For the three amnesic agents utilized, the age and strain difference will be considered with respect to (a) differences in 5-HT metabolism in the synaptic area; (b) alterations in protein synthesis in these regions measured by the incorporation of C^{14}-leucine into proteins and (c) the time relationship between these two events. Under these conditions, effects of either nicotine, cotinine, and 3-pyridylacetic acid will be determined with the former compound administered in doses up to 1 mg/kg body weight and the latter two compounds administered up to doses of 0.3 mg/kg.

A final series of studies will concern (3) The cellular effects of nicotine and active metabolites during late development. It has been shown that aging, particularly in rodents, contributes appreciably to the changes in retentive ability for retentive behavior and to the degree to which the potency of certain amnesic stimuli may be manifest. It is the purpose of these series of experiments to inter-relate the effects of nicotine, cotinine and 3-pyridylacetic acid, based

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9. continued:

upon dose response elaboration, to the regional changes in 5-HT metabolism and synaptic protein synthesis in old mice. Mice from the three designated strains will be maintained in laboratory colonies until the age of 120 days, when behavioral testing will establish: (a) changes in their conditioning for passive avoidance behavior, (b) changes in their susceptibility to the three amnesic events to be utilized, and (c) changes in endogenous 5-HT and protein synthesis. It is hypothesized that aging will contribute to reduced resistance to stimulus-induced amensia, measured both behaviorally with the conditioning technique described and biochemically by the changes in 5-HT metabolism and synaptosomal protein synthesis. Under these conditions, it is hypothesized that the dose, duration of effect and potency of nicotine and active metabolites will be altered so that such effects may be more apparent in aged mice.

These relationships will be studied in several experiments that allow for a detailed statement of the relationship between both early development as well as aging as contributants to the nicotine mediated changes in memory consolidation and the biochemical events requisite for that process.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Two air-conditioned laboratories with adjoining vivarium facilities are currently in use by the investigator. All equipment necessary for the behavioral and biochemical procedures involved with this proposal are available and no additional equipment needs are anticipated for the duration of this project.

11. Additional facilities required:

NONE

12. Biographical sketches of investigator(s) and other professional personned (append):

See Page 3a.

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available.

See Page 3b.

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WALTER B. ESSMAN

Education:

Ph.D. - University of North Dakota, 1957 (Major: Psychology; Minor: Medical Sciences)

M.D. - (Cum Laude) - University of Milan, 1972 - when did he take time out to earn this?

M.A. - University of North Dakota, 1955

B.A. - New York University, 1954

Experience:

Professor (Psychology, Biochemistry), Queens College of the City University of New York, 1967 - Present.

Associate Professor, Queens College of the City University of New York, 1965-1966.

Assistant Professor, Queens College of the City University of New York, 1962-64.

Research Professor, Neurology, Mt. Sinai School of Medicine, New York, 1972 - Present.

Research Associate, Laboratory of Neurochemistry, Mt. Sinai School of Medicine, New York, 1966 - 72.

Research Fellow, Laboratory of Neurochemistry, Mt. Sinai Hospital, New York, 1964 - 66.

Research Assistant Professor, Dept. of Rehabilitive Medicine, Albert Einstein College of Medicine, 1962-63.

Research Associate, Dept. of Physiology, Albert Einstein College of Medicine, 1961-63.

Senior Post-Doctoral Fellow, Neurophysiology, Albert Einstein College of Medicine, 1959-61.

Director, Psychophysiological Research, U.S. Army Surgical Research Unit, 1958-59.

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13. Publications (5 most recent):

1. Essman, W.B. Brain 5-hydroxytryptamine and memory consolidation. In: Gessa, G. L., and Sandler, M. Advances in Biochemical Psychopharmacology, Volume 11, Serotonin: New Vistas. Biochemistry and Behavioral and Clinical Studies. Raven Press, 1974, Pgs. 265-274.

2. Essman, W.B. Amine mediated retrograde amnesia: factors effecting cerebral protein synthesis. In: Bogoch, S. (Ed). Biological Diagnosis of Brain Disorders. N.Y.: Spectrum Publications, 1974.

3. Essman, W.B. Effects of ECS on cerebral protein synthesis. In: Fink, M., Kety, S.S., McGaugh, J., & Williams, T. (Eds.). The Psychobiology of Convulsive Therapy. Washington, D.C.; V.H. Winston & Sons, 1974, Pp. 237-249.

4. Essman, W.B. Pharmacological alterations of the retrograde amnesic effect of electroconvulsive shock: the modification of forebrain 5-hydroxytryptamine in mice. Pharm. Res. Commun., 1973, 5: 295-302.

5. Essman, W.B. Neurochemistry of Cerebral Electroshock. New York: Spectrum Publications, 1973.

Relevant Publications: 1971-1973

1. Essman, W.B. and Nakajima, S. Experimentally-induced retrograde amnesia: some neurochemical correlates. In: Essman, W.B. & Nakajima, S. (Eds.). Current Biochemical Approaches to Learning and Memory. N.Y.: Spectrum Publications, 1973, Pp. 159-188.

2. Essman, W.B. Effetti dell'elettroshock sulla neurochimica del sistema nervaso centrale, 1. Rass. Clin. Scient., 1972, 48: 361-370.

3. Essman, W.B. Biphasic effects of nicotine on ECS-induced retrograde amnesia in mice. Psychol. Rep., 1973, 32: 658. (with S.G. Essman).

4. Essman, W.B. Retrograde anmesia and cerebral protein synthesis: initiation and inhibition by 5-Hydroxytryptamine. Totus Homo, 1972, 4: 61-67.

5. Essman, W.B. Age-dependent effects of 5-hydroxytryptamine upon memory consolidation and protein synthesis. Pharmacol. Biochem. & Behavior, 1973, 1: 7-14.

6. Essman, W.B., Whittaker, V.P. and Dowe, G.H.C. The isolation of pure cholinergic synaptic vesicles from the electric organs of elasmobranch fish of the family Torpedinidae. Biochem. J., 1972, 128: 833-846.

7. Essman, W.B. Discussion of neurochemistro of benzodiazepines. In: Garattini, S., Mussini, E., & Randall, L.O. (Eds.). The Benzodiapzpines. N.Y.: Raven Press, 1973, Pp. 281-283.

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8. Essman, W.B. Nicotine-related neurochemical changes: some implications for motivational mechanisms and differences. In: Dunn, W.J., Jr., (Ed.). Smoking Behavior, 1973, Pp. 51-65.

9. Essman, W.B. Neurochemical modulation of experimentally induced retrograde amnesia. Confinia Neurol., 1973, 35: 1-22.

10. Essman, W.B. Changes in the amnesic and aversive properties of avoidance conditions with chlordiazepoxide. Pharmacol. Biochem. & Behavior, 1973, 1: 125-128.

11. Essman, W.B. Subcellular actions of benzodiazepines. In: Garattini, S., Mussini, E. & Randall, L.O. (Eds.). The Benzodiazepines. N.Y.: Raven Press, 1973, Pp. 177-190.

12. Essman, W.B. Neurochemical changes in ECS and ECT. Seminars in Psychiatry, 1972, 4: 67-79.

13. Essman, W.B. and Heldman, E. Impairment of avoidance acquisition and altered regional brain amine levels in mice with eremic endotoxemia. Physiol. Behav., 1972, 8: 143-146.

14. Essman, W.B. Changes in cholinergic activity and avoidance behavior by nicotine in differentially housed mice. Int. J. Neurosci., 1971, 2: 199-206.

15. Essman, W.B. and Essman, S.G. Cholinergic mechanisms and avoidance behavior acquisition: effects of nicotine in mice. Psychol. Rep., 1971, 29: 987-993.

16. Essman, W.B., Essman, S.G. and Golod, M.I. Metabolic contributions to gastric ulcerogenesis in mice. Physiol. Behav., 1971, 7: 509-516.

17. Essman, W.B., Barker, L.A., Dowdall, M. & Whittaker, V.P. The compartmentation of acetylcholine in cholinergic nerve terminals. In: Heilbonn, E., and Winter, A. (Eds.). Drugs and Cholinergic Mechanisms in the C.N.S. Stockholm: Research Institute of National Defense, 1971.

18. Essman, W.B. The role of biogenic amines in memory consolidation. In: Adam, G. (Ed.). The Biology of Memory. N.Y.: Plenum Press, 1971, Pp. 213-238.

19. Essman, W.B. Isolation-induced behavioral modification: some neurochemical corellates. In: Sturman, M.G., McGinty, D.J. and Adinolfi, A.M. (Eds.). Brain Development and Behavior. N.Y.: Academic Press, 1971, Pp. 265-276.

20. Essman, W.B. Drug effects and learning and memory processes. In: Garattini, S. and Shore, P. (Eds.). Advances in Pharmacology and Chemotherapy. N.Y.: Academic Press, 1971, Pp. 241-330.

21. Essman, W.B. Behavioral correlates of acute renal failure. In: Coletti, R.B. and Krueger, K.K. (Eds.). Proc. of Workshop on Behavioral Bioassay in Uremia. Washington, D.C., U.S. Gov't Printing Office, 1971, Pp. 18-30.

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8. Essman, W.B. Nicotine-related neurochemical changes: some implications for

22. Essman, W.B. Drugs affecting facilitation of learning and memory. In: Rubin, A.L. (Ed.). Search for New Drugs. N.Y.: Dekker, 1972, 385-406.

23. Essman, W.B. Contributions of differential housing to brain development: some implications for sleep behavior. In: Clemente, C.D., Purpura, D.P., and Mayer, F.E. (Eds.). Sleep and the Maturing Nervous System. N.Y.: Academic Press, 1971, Pp. 99-107.

24. Essman, W.B. Memory and amnesia changes induced by nicotine and its metabolites. In: Votava, Z. (Ed). Neuropsychopharmacology, 1971.

25. Essman, W.B. Metabolic and behavioral consequences of nicotine. In: Smith, W.L. (Ed.). Cerebral Function Development and Drug Action. Springfield: Chas. Thomas, 1972, Pp. 273-287.

26. Essman, W.B. Neurochemical changes associated with isolation and environmental stimulation. Biol. Psychiat., 1971, 3: 141-147.

27. Essman, W.B., Prescott, J.W. and Heath, R.G. Early somatosensory deprivation as an ontogenetic process in the abnormal development of the brain. Ann. N.Y. Acad. Sci., 1971.

28. Essman, W.B. Psychopharmacology. In: Eysenck, H.J. (Ed.). Handbook of Abnormal Psychology. London: Pittman, 1972, Pp. 634-676.

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R: REDACTED MATERIAL

14. First year budget:

	% Time	Amount
A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)		
Dr. Walter B. Essman		REDACTED
Technical		
Traum, John - Technical Assistant Rosenthal, Richard -- Assistant		REDACTED
+ 20% Fringe Benefits		REDACTED
Sub total for A		
B. Consumable supplies (by major categories)		
Animal purchases		$ 800.
" cleaning, bedding		600.
" chemicals, glassware		840.
disposable cages		450.
Sub total for B		$ 2,690.
C. Other expenses (itemize)		
6th Annual Winter Conference for Brain Research, January, 1975, Vail, Colorado Endocrine Society, Chicago, Illinois, June, '75 American College of Neuropsychology, San Juan, Puerto Rico, December '75		
Sub total for C		$ 1,100.
Running Total of A+B+C		$20,170.
D. Permanent equipment (itemize)		
NONE		
Sub total for D		----
E. Indirect costs (15% of A+B+C)	E	$ 3,026.
Total Request		$23,196.

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16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
"Metabolic Response to Stress -- Tobacco Smoke Interactions	RF-09165 C.T.R. #836A	$40,000.	10/1/73 - 9/30/74
"Role of Nicotine Action Upon Memory Consolidation	RF-09104 C.T.R. #632BR1 (Continuation of carry over funds)	$14,911.79	2/1/74 - 12/31/74

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Checks payable to:

Research Foundation of C.U.N.Y.

Mailing Address for checks:
Mr. Paul Segall, Comptroller
Research Foundation of C.U.N.Y.
1411 Broadway
New York, New York 10018

Principal Investigator

Typed Name: Walter B. Essman, M.D., Ph.D.

Signature: Walter B. Essman Aug 5, 1974

Telephone: (212) 544-6421

Responsible Officer of Institution

Typed Name: 1. Hannah Petzenbaum
2. David H. Speidel

Title: 1. Research Fndtn.- Q.C.
2. Asst. Dean of Faculty Q.C.

Signature: 1. [illegible] Date: 8/5/74
2. [illegible]

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